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Comparison of tocilizumab and intravenous immunoglobulin treatment in intensive care unit patients with COVID-19 who developed cytokine storm: A single-center retrospective study

Tocilizumab versus ivig

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Abstract

Aim: Coronavirus disease 2019 (COVID-19) may trigger a severe inflammatory response. In the present study, the effects of tocilizumab and intravenous immunoglobulin (IVIG) on mortality in COVID-19 patients with cytokine storms were examined and compared.

Material and Methods: This retrospective study included all COVID-19 patients who were diagnosed and followed in the intensive care unit between April 2020 and May 2022. The patients were divided into two groups depending on whether they were receiving IVIG or tocilizumab treatment. In addition to the patients' demographic information, the 28-day mortality was recorded. Their PaO2/FiO2 ratio, CRP, procalcitonin, lymphocyte, ferritin, and D-dimer levels were also recorded before drug administration and on the first day, third day, and first week following the drug administration.

Results: Of the 73 patients included in this study, 43 (59%) received tocilizumab (Group T), while 30 (41%) received IVIG treatment (Group IVIG). No significant statistical differences were detected between the groups in terms of demographic data, pre-drug inflammatory parameters, improvement in PaO2/FiO2 ratios, and 28-day mortality. The rate of change in CRP levels was significantly higher in Group T than in Group IVIG on day 3 ($p=0.010$) and in the first week ($p=0.001$). The improvement in ferritin levels in the first week was significantly higher in Group T ($p=0.018$).

Discussion: No significant difference was detected between the effects of IVIG and tocilizumab on mortality in COVID-19 patients with cytokine storm. However, tocilizumab suppressed inflammation more strongly than IVIG.

Keywords

Ards, Covid-19, Cytokine Storm Syndrome, Ivig, Tocilizumab

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This study was approved by the Ethics Committee of Inonu University (Date: 2023-10-31, No: 2023/4941)

Introduction

The coronavirus pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which results in severe acute respiratory failure, became a significant public health concern in the last three years. SARS CoV-2 might cause damage and death in many organs, especially the lungs, by targeting angiotensin-converting enzyme (ACE)-2 receptors [1, 2]. The term 'cytokine storm' refers to a condition wherein cytokines are released in excessive amounts into the systemic circulation and are held responsible for the abovementioned damages [1, 3]. In the final stage of the disease, it was observed that systemic levels of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-2, IL-6 and IL-7, tumor necrosis factor (TNF)-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 1-α, C-reactive protein (CRP), ferritin, and D-dimer are significantly increased [4]. Steroids, hydroxychloroquine, IL-6 and IL-1 inhibitors, TNF-α inhibitors, and Janus kinase inhibitors have been suggested as potential treatment agents [5, 6].

Previous studies involving tocilizumab, an IL-6 receptor blocker, have produced conflicting results [7, 8]. Intravenous immunoglobulin (IVIG) is an immunomodulatory treatment utilized in various inflammatory diseases. Dynamic cytokine storms and T-cell lymphopenia have been linked to COVID-19 severity [9].

In our clinic, tocilizumab was administered to patients who developed cytokine storms because of COVID-19. However, in cases where tocilizumab was not available or where there was a suspected or confirmed bacterial infection, IVIG was used instead. No study was found in the literature comparing the effects of tocilizumab and IVIG on inflammation, particularly mortality, in COVID-19 patients requiring intensive care and experiencing cytokine storms. Therefore, this retrospective study aimed to compare the efficacy of tocilizumab and IVIG treatments in patients who were followed up in the tertiary intensive care unit and developed cytokine storms because of COVID-19.

Material and Methods

Study Design

The present study employed a single-center retrospective design and was conducted at a tertiary university hospital following approval by the Inonu University Scientific Research and Publication Ethics Board and the Health Sciences Non-invasive Clinical Research Ethics Board, with decision number 2023/4941 on 31 October 2023. Patients diagnosed with COVID-19 between April 2020 and May 2022, who were followed up and treated in the intensive care unit and developed a cytokine storm, were included in the study.

Inclusion criteria. Patients whose COVID-19 diagnosis was confirmed through clinical, laboratory, and imaging methods, who were aged 18 years and older, and who developed a cytokine storm were included in the study. The development of a cytokine storm was determined based on increasing CRP, IL-6, ferritin, and D-dimer levels and decreasing lymphocyte count compared with the patient's baseline values (or values before the onset of the disease, if available).

Exclusion Criteria

Patients who received immunomodulatory/immunosuppressant treatments other than tocilizumab and IVIG, those who received tocilizumab and IVIG simultaneously or sequentially, who were pregnant, who died during treatment, who had solid organ transplantation and who had other underlying or concomitant inflammatory diseases were excluded from the study.

The diagnosis of COVID-19 in our hospital and clinic was made based on the SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) test conducted on nasopharyngeal swab samples and thorax CT findings during the COVID-19 pandemic if there were associated symptoms. Patients with COVID-19 who developed a cytokine storm were categorized into two groups based on whether they received tocilizumab or IVIG treatment.

Group T (n=43): This group comprised individuals who received tocilizumab alongside standard treatment (1 mg/kg/day methylprednisolone, low-molecular-weight heparin, empiric antibiotic, mucolytic, and proton pump inhibitor). Tocilizumab was administered in our clinic in two consecutive doses during the pandemic, with a 12- to 24-hour interval, based on the patient's weight (8 mg/kg/day, max 800 mg).

Group IVIG (n=30): This group consisted of individuals who received IVIG as well as standard treatment. IVIG treatment was given at a dose of 0.4 mg/kg/day (total 2 g/kg) for five consecutive days in our clinic.

In our clinic, tocilizumab treatment was not used in the presence of neutropenia (0.5x10^3 cells/ul), thrombocytopenia (50x10^3 cells/ul), gastrointestinal perforation, and active bacterial infection. Procalcitonin levels were utilized to assess active bacterial infections, along with clinical symptoms and demonstration of the infectious agent in gram staining or culture in microbiological samples. Tocilizumab was not administered to any patient with a procalcitonin level above 2 ng/ml. In this clinic, patients were treated with IVIG. Additionally, hepatitis markers were tested in all patients to detect latent hepatitis B infection or carrier status.

The primary outcome of the study was 28-day mortality, while the secondary outcome was the change in inflammatory parameters.

Patient data were obtained retrospectively through the electronic system and patient follow-up cards. Demographic characteristics, age, gender, comorbidities, clinical status, inflammatory parameters (CRP, ferritin, D-dimer, procalcitonin, fibrinogen, IL-6), PaO2/FiO2 ratio, need for mechanical ventilation and 28-day mortality were recorded. Disease severity was measured using the Acute Physiology and Chronic Health Evaluation II (APACHE II), while organ dysfunction was determined using the SOFA Score.

Statistical Analysis

The IBM SPSS Statistics 22 program was used for statistical analysis. Before conducting the analyses, the Shapiro–Wilk test was utilized to examine whether the data met the assumption of normality to select analyses that were appropriate for the data. In cases where the data met the normality assumption, the independent samples t-test was used for between-group comparisons, while the Mann–Whitney U test was used in cases where it was not met. The homogeneity of variances assumption for the t-test in independent groups was examined using the Levene's test. Within-group comparisons were conducted using the Wilcoxon test. Gender, comorbidities, pulse steroid intake, oxygen delivery method, and 28-day mortality were evaluated with the chi-square test, and p<0.05 was considered significant.

Ethical Approval

This study was approved by the Ethics Committee of Inonu University (Date: 2023-10-31, No: 2023/4941).

Results

During the study period, a total of 547 patients were treated in the COVID-19 intensive care unit (Figure 1). No statistically significant differences were detected between the groups in terms of age, gender, comorbidities, APACHE and SOFA scores, time from hospital admission to medication administration, oxygen treatment methods, and 28-day mortality. However, patients in Group IVIG received more steroids (Table 1).

There were no statistically significant differences between the groups in PaO2/FiO2 ratios, D-dimer levels, and lymphocyte levels. Notably, CRP levels were significantly lower in Group T than in Group IVIG on the third day and in the first week after the administration of the drug. Procalcitonin levels were statistically and significantly higher in Group IVIG than in Group T only during the first week. Ferritin levels were significantly higher in Group T before and on the first and third days after the drug administration, with no significant difference detected between the groups during the first week. IL-6 levels were significantly higher in Group T on the third day and during the first week (Table 2).

The values before the administration of the drug were compared with the values on the first day, third day, and first week after the administration. The PaO2/FiO2 ratios were found to be significantly higher on the third day and first week in the groups (p=0.018 and p=0.009, respectively, for Group T and p=0.035 and p=.017, respectively, for Group IVIG). The CRP levels were higher in Group T on the third day and in the first week (p=0.001 and p=0.001, respectively), while Group IVIG exhibited a significant decrease in the first week (p=0.014). No significant changes were detected in procalcitonin levels in the groups. Lymphocyte levels decreased significantly on the first day in Group T (p=0.002) and on Day 3 in Group IVIG when compared to before the drug administration (p=0.008). The ferritin levels increased in Group T on the first day and decreased in the first week compared to pre-administration (p=0.031 and p=0.048, respectively). The D-dimer levels were significantly higher on the third day and in the first week in Group T than before the drug administration (p=0.002 and p=0.008, respectively). IL-6 levels increased significantly with tocilizumab in all periods when compared to before administration (day 1: p=0.037, day 3: p=0.001, and week 1: p=0.001, respectively, in Group T).

When comparing changes in inflammatory parameters relative to values before drug administration, significant differences were observed between the groups. The rate of change in CRP levels was significantly higher in Group T than in Group IVIG on Day 3 (p=0.010) and during the first week (p=0.001). Similarly, the rate of change in IL-6 levels was significantly elevated in Group T compared to Group IVIG on Day 3 (p=0.001) and during the first week (p=0.004). The improvement in ferritin levels was

Table 1. Demographic data of patients

	Group Tocilizumab (n=43)	Group IVIG (n=30)	P value
Age (year)	65.14 ± 14.91	63.83 ± 13.21	0.533
Gender (M/F)	37/6	21. 9	0.097
Co-existing diease			
Diabetes mellitus	17	9	0.365
Hypertension	17	12	0.968
Coronary arter disease	8	10	0.154
Malignancy	3	4	0.367
Renal failure	4	2	0.319
Receiving pulsed steroid	16	19	0.029*
Oxygen management			0.850
Nasale cannula/face mask	2	2	
HFNC/NIV	30	19	
Invasive mechanical ventilation	11	9	
Time from diagnosis to drug administration	5.48 ± 3.52	5.47 ± 4.15	0.654
Time from ICU admission to drug administration	2.65 ± 2.30	1.43 ± 0.81	0.027*
APACHE before drug	15.86 ± 7.19	14.87 ± 6.20	0.639
SOFA before drug	4.67 ± 2.81	4.50 ± 2.53	0.852
SOFA after 1st week drug	6.44 ± 4.57	6.32 ± 3.75	0.837
Mortality (28 day)	30	20	0.668
PaO2/FiO2 before drug	70.86 ± 26.81	82.65 ± 53.01	0.526
PaO2/FiO2 1st day after drug	74.67 ± 31.50	102.00 ± 69.78	0.060
PaO2/FiO2 3rd day after drug	84.86 ± 52.54	108.73 ± 63.02	0.122
PaO2/FiO2 1st week after drug	93.17 ± 46.80	126.99 ± 79.99	0.140

HFNC: High-Flow Nasal Cannula, NIV: Non-Invasiv Ventilation, ICU:Intensive Care Unit, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assesment, FiO_2: Fraction Of İnspired Oxygen, PaO_2:Partial Pressure Of Arterial Oxygen

Table 2. Comparison of inflammatory markers of groups

	Normal range	Group T (n=43)	Group IVIG (n=30)	P value
CRP before drug	0-0.35 mg/dl	12.25 ± 6.28	11.49 ± 6.00	0.609&
CRP 1st day after drug		10.69 ± 6.80	10.98 ± 6.46	0.854&
CRP 3rd day after drug		4.56 ± 3.95	9.05 ± 8.11	0.007*
CRP 7tht day after drug		1.87 ± 2.85	5.92 ± 6.10	0.001*
Procalcitonin before drug	0-0,5 ng/mL	0.37± 0.36	4.28 ± 12.26	0.724
Procalcitonin 1st day after drug		1.26 ± 5.26	4.78 ± 11.90	0.809
Procalcitonin 3rd day after drug		2.86 ± 14.65	3.18 ± 7.93	0.153
Procalcitonin 7tht day after drug		0.58± 1.59	1.92 ± 3.19	0.023*
Lymphocytes before drug	1,3-3,5 10^3/uL	730.47 ± 326.93	995.33 ± 497.34	0.343
Lymphocytes 1st day after drug		607.56 ± 276.68	898.80 ± 416.72	0.226
Lymphocytes 3rd day after drug		659.76 ± 363.80	770.03 ± 303.50	0.504
Lymphocytes 7tht day after drug		858.12 ± 454.10	822. 24 ± 407.66	0.414
Ferritin before drug	22-322 ng/mL	946.02 ± 523.47	587.90 ± 428.51	0.002*
Ferritin 1st day after drug		1055.86 ± 518.52	662.43 ± 477.39	0.002*
Ferritin 3rd day after drug		1023.32 ± 524.96	565.47 ± 448. 16	0.001*
Ferritin 1st week after drug		738.16 ± 492.11	631.90 ± 449.74	0.455
IL-6, before drug		183.47 ± 215.54	302.93 ± 934.16	0.237
IL-6, 1st day		402.99 ± 520.22	222.57 ± 416.58	0.099
IL-6, 3rd day		1020.73 ± 1369.17	180.43 ± 350.68	0.001*
IL-6, 1st week		1579.73 ± 1890.90	340.37 ± 596.03	0.001*
D-dimer, before drug	0-0,55 mg/L	3.77 ± 5.45	7.47 ± 18.82	0.658
D-dimer, 1st day		5.01 ± 9.76	9.75 ± 19.46	0.937
D-dimer, 3rd day		4.98 ± 4.43	7.81 ± 18.14	0.835
D-dimer, 1st week		5.24 ± 3.73	10.87 ± 19.99	0.753

&: ındependent sample t test, others Mann Whitney U test

significantly higher in Group T during the first week (p = 0.018). However, the change rates in PaO2/FiO2, procalcitonin, and D-dimer levels did not differ significantly between the groups.

Discussion

Various treatment modalities, including corticosteroids and inhibitors targeting mediators such as IVIG, IL-1, IL-6, TNF, IFN-γ, and Janus kinase have been utilized in the suppression or treatment of the cytokine storm associated with COVID-19 [10- 14]. In the present study, patients who were followed up in the intensive care unit because of COVID-19-related cytokine storm and were treated with tocilizumab or IVIG were evaluated retrospectively. First, it was retrospectively confirmed that all patients included in the present study experienced a cytokine storm, characterized by increased CRP, ferritin, and D-dimer levels and decreased lymphocyte values. Furthermore, demographic characteristics, ARDS severity, disease severity, time from hospitalization to medication administration, and oxygen support treatments were similar in the groups. No differences were detected in terms of mortality between those treated with tocilizumab and those given IVIG.

High IL-6 levels have been shown to cause damage to pulmonary tissues and facilitate the spread of the virus [15]. Some studies have reported that they detected no significant differences in mortality rates between patients who were given tocilizumab and those who were not, and the mortality rate was reported to be between 24% and 34% [7, 12]. However, it was observed in these studies that all hospitalized COVID patients were included, critically ill patients were in the minority, and intensive care admission was associated with mortality. In another study, it was reported that mortality was high in patients with high IL-6 levels who were not treated with tocilizumab and in patients with low IL-6 levels who were treated with tocilizumab. In the same study, when only those given tocilizumab were considered, it was found that 24 out of 59 cases resulted in mortality [16]. However, the PaO2/FiO2 ratios and inflammatory markers of the patients who were included in the present study were more severe than in the abovementioned studies. In the study conducted by Saffo et al., 30-day survival was reported to be 40%; in other words, there was 60% mortality [17]. The findings of the previous study are compatible with the results of the present study.

IVIG stimulates regulatory T-cells, regulates the complement system, and clears cytokines. It was also suggested that it might inhibit cytokine production and trigger apoptosis in dendritic cells, natural killer cells, macrophage T and B lymphocytes [18]. Among previous studies that investigated the effects of IVIG on mortality in patients with a cytokine storm because of COVID-19, some reported that IVIG had no effects on mortality, while others reported that it reduced mortality [14, 19, 20]. However, studies have also emphasized that IVIG is effective if given early before the disease reaches the severe stage [21]. A recent meta-analysis reported that IVIG did not reduce mortality, but high doses had positive effects on mortality in patients with severe COVID-19 [22].

In the literature review, no study that directly investigated the effects of tocilizumab and IVIG on mortality was found. The research closest to the present study was a retrospective study conducted by Zantah et al. on 84 patients, comparing anakinra/IVIG with tocilizumab. Although no differences were detected between the groups in terms of mortality, the total mortality rate of the groups was reported to be 19% [23]. In another prospective study, all patients were given tocilizumab, but IVIG was added to the treatment modality for those whose ferritin levels continued to increase despite tocilizumab use. The mortality rate was reported to be 15.4% in the group that received only tocilizumab and 38.46% in those that received IVIG along with tocilizumab [24]. In our study, the mortality rate among patients treated with tocilizumab was approximately 70%. The higher mortality rate in the present study than in the literature was attributed to the fact that only patients who needed intensive care were included in the study. Moreover, the patients had worse PaO2/FiO2 ratios and other inflammatory parameters, leading to the later administration of immunosuppressants compared to other studies.

Corticosteroids are also employed to attenuate the inflammatory response in COVID-19 patients [25]. Notably, our study found that more pulse steroids were given to those who received IVIG, which led to the conclusion that steroids were added to more patients in the IVIG group to increase immunosuppression due to tocilizumab's earlier and more potent immunosuppressive effect compared to IVIG.

Previous studies have demonstrated improvements in inflammatory mediators and PaO2/FiO2 ratios after tocilizumab and IVIG administration [10, 21, 22, 24, 30]. However, no significant differences were detected in inflammatory marker levels (except ferritin) before and after tocilizumab or IVIG administration. Similar increases in PaO2/FiO2 ratios were observed three days and one week after tocilizumab and IVIG administration. Notably, the decrease in CRP level was earlier and greater in patients treated with tocilizumab. Ferritin levels were higher before drug administration in the tocilizumab group on the first and third days, subsequently declining to similar levels in the two groups, albeit with a greater decrease observed in the tocilizumab group in Week 1.

Although no statistically significant differences were observed in procalcitonin levels until the first week, according to our laboratory reference ranges, values above 2 ng/ml require evaluation in favor of bacterial infection. Therefore, although the average value was below 0.5 in individuals treated with tocilizumab, it was approximately 4.5 in those treated with IVIG. This occurred because tocilizumab is contraindicated in the presence of bacterial infection, necessitating the use of IVIG as an alternative treatment agent in this patient group. The observed increase in IL-6 levels following the administration of tocilizumab was consistent with the literature data [10].

Study limitations. The present study had some limitations. It was conducted in one center retrospectively, the number of patients was low and individuals who did not take the featured medications were not included.

Conclusion

Tocilizumab and IVIG had similar effects on mortality among patients who developed cytokine storms and were followed and treated with the same approach. Both treatments improved oxygenation. However, the suppression of inflammation was noted to be earlier and more significant with tocilizumab. In conclusion, when tocilizumab is unavailable or cannot be used, IVIG should be considered as an alternative agent or treatment option. Conversely, when IVIG is not accessible or suitable, tocilizumab may be administered with comparable effectiveness.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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